Type 1 Diabetes Mellitus and Pregnancy

Roberto Vargas, John T. Repke, MD, FACOG, Serdar H. Ural, MD, FACOG

Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Penn State University College of Medicine, Hershey, PA

Diabetes complicates up to 10% of all pregnancies in the United States. Of these, 0.2% to 0.5% are patients with type 1 diabetes mellitus (T1DM). Pregnancies affected by T1DM are at increased risk for preterm delivery, preeclampsia, macrosomia, shoulder dystocia, intrauterine fetal demise, fetal growth restriction, cardiac and renal malformations, in addition to rare neural conditions such as sacral agenesis. Intensive glycemic control and preconception planning have been shown to decrease the rate of fetal demise and malformations seen in pregnancies complicated by T1DM. Recent advances in insulin formulations and delivery methods have increased the number of options available to the obstetric team. Insulin regimens should be tailored to each individual patient to maximize compliance and ensure proper glycemic control. Intensive preconception counseling with frequent follow-up visits emphasizing tight glucose control is recommended for adequate management.
[Rev Obstet Gynecol. *2010;3(3):92-100 doi: 10.3909/riog0114*]

Key words: Insulin • Nephropathy • Type 1 diabetes mellitus • Pregnancy • Diabetic ketoacidosis

Type 1 diabetes mellitus (T1DM), previously known as juvenile onset diabetes or insulin-dependent diabetes mellitus (IDDM), accounts for 5% to 10% of diagnosed diabetes in the United States.[1] This subclass of diabetes mellitus develops as a result of an autoimmune response directed against insulin-producing β cells, located in the pancreas. Due to the destruction of these cells, patients with T1DM require insulin replacement to achieve euglycemia. Onset of this disease generally occurs before age 30, and thus can affect women during their reproductive years. Between 0.2% and 0.5% of all pregnancies in the United States are complicated by T1DM each year.[2,3]

Before the implementation of insulin therapy, infertility was the most common consequence of diabetes mellitus on reproductive-age women, and when pregnancy did occur, fetal and neonatal mortality was as high as 60%. Aggressive maternal-fetal management, advances in insulin therapy, and improvements in neonatal intensive care units have decreased this figure to 2% to 5%.[3] The realization that improved perinatal outcomes are directly correlated with improved glycemic control and inversely correlated with existing end-organ damage led to the development of the White classification system of diabetes during pregnancy (Table 1).[4]

The realization that improved perinatal outcomes are directly correlated with improved glycemic control and inversely correlated with existing end-organ damage led to the development of the White classification system of diabetes during pregnancy.

Pathophysiology

T1DM is caused by an immune-mediated destruction of insulin-producing β cells, located in the pancreatic islets of Langerhans. Although the exact cause of this disease still eludes scientists, it is known that a general inflammatory state, termed *insulitis*, precedes overt diabetes. During this state of inflammation, macrophages, B lymphocytes, CD4+, and CD8+ T lymphocytes can be seen to infiltrate the islets of Langerhans. A complex cycle of antigen presentation and propagation leads to an eventual accumulation of CD8+ lymphocytes, and gradual destruction of insulin-producing β cells.[5] This decline in β-cell mass eventually leads to an insulin-deficient state, causing hyperglycemia in the affected patient.

Pregnancy itself is usually regarded as a diabetogenic state in which postprandial glucose levels are elevated and insulin sensitivity is decreased.[4] Classically, the decreased response to insulin activity observed in pregnancy has been attributed to increases in hormones such as cortisol, progesterone, estrogen, prolactin, and human placental lactogen.[6] Most recently, new molecules such as leptin, tumor necrosis factor-α (TNF-α), and resistin have been implicated in this matter. Kirwan and colleagues[7] showed that TNF-α is the strongest independent predictor of insulin sensitivity during the late gestational period. In vitro studies showed that TNF-α disrupted insulin signaling and inhibited glucose uptake.[7] This study attributed the rise of TNF-α to increased placental production with advancing gestational age (Table 2).

Fluctuations in insulin sensitivity during pregnancy, mostly due to changing hormone levels, complicate insulin replacement in gravid Type 1 patients with diabetes. In 1984, Weiss and Hofmann[8] presented data showing a 12% decrease in insulin requirements between 10 and 17 weeks gestation. Following the 17th week of gestation, the total insulin requirements increase by more than 50%.[8] Although these data presented important fluctuations in insulin requirements and physiologic changes during pregnancy, the limited study size and different insulin regimens used in

Table 1
Modified White Classification System

Class	Onset (age)	Duration	Insulin	Criteria
A_1	Any	Any	No	Gestational diabetes
A_2	Any	Any	Yes	Gestational diabetes
B	>20	<10	Yes	Benign retinal and renal findings
C	10-19	10-19	Yes	Age of onset 10-19 years *or* duration 10-19 years
D	<10	>20	Yes	Age of onset < 10 *or* duration > 20 years
F	Any	Any	Yes	Nephropathy (> 500 mg/day protein)
R	Any	Any	Yes	Proliferative retinopathy
RF	Any	Any	Yes	Retinopathy and nephropathy
T	Any	Any	Yes	Renal transplant patient
H	Any	Any	Yes	Cardiovascular disease

Data from White P.[4]

Table 2
Molecular Mediators of Insulin Resistance

Enzyme	Molecular Action
Progesterone	↓ Peripheral glucose uptake
Estrogen	↓ Peripheral glucose uptake
Cortisol	↑ Gluconeogenesis
	↓ Insulin sensitivity
Prolactin	↑ Glucose
	↑ Mammary glandular tissue
	↓ GnRH response
Human placental lactogen	↑ Lipolysis
	↑ FFA
	↑ Mammary glandular tissue
	↓ Insulin sensitivity
Insulinase	↑ Insulin degradation
TNF-α	↓ Insulin receptor activity

FFA, free fatty acid; GnRH, gonadotropin-releasing hormone; TNF-α, tumor necrosis factor-α.
Data from Gabbe SG et al.[6]

the study limit the statistical significance. A recent prospective study involving 65 T1DM patients further characterized insulin requirements throughout pregnancy. Using assays and glycemic control parameters not previously available, García-Patterson and colleagues[9] were able to follow total insulin requirements, insulin requirements based on weight, while controlling for glycosylated hemoglobin levels (HbA_1C), and mean blood glucose levels. As previously suggested by Weiss and Hofmann, 2 peaks in insulin requirements, one at week 9 and the other at week 37, were observed.[8] After the initial peak at around 9 weeks, a slow decrease in insulin requirements was noted. The average nadir point was documented to be at 16 weeks, with a subsequent rise until 37 weeks gestation.[9]

Of note, a recent Danish prospective study by Nielsen and colleagues[10] showed an increase in C-peptide during pregnancy in diabetic patients. This study consisted of 90 gravid T1DM patients with a median duration of diabetes of 17 years (1-35 years). Even in patients with undetectable C-peptide prior to pregnancy, a rise in serum levels was noted. A median change in C-peptide levels of 50% was reported.[10] These data provide yet another factor that could be contributing to the variability of insulin requirements throughout the progression of pregnancy.

Complications

Hypoglycemia

Hypoglycemia, particularly nocturnal, is a common occurrence with classic insulin replacement therapies.[3] Increasing insulin requirements, alongside tight glycemic control, increase the propensity for episodes of insulin overdose. Counter-regulatory hormones, such as cortisol, glucagon, and epinephrine, which protect against hypoglycemia, are blunted in pregnancy. The warning signs of hypoglycemia, such as tachycardia, diaphoresis, weakness, and pallor, occur in response to these hormones. In addition to the blunted response seen during pregnancy, patients with T1DM have a reduced glucagon and cortisol response inherent to the disease. The combination of these phenomena can mask hypoglycemia.[11] Patients and family should be counseled on the signs and symptoms of hypoglycemia and instructed to give the patient a glass of milk or juice when concerned about low blood sugar.

Diabetic Ketoacidosis

Insulin deficiency creates a metabolic state that is interpreted as starvation by the body. In response to the decreased intracellular glucose concentrations, the body is forced to tap into energy stores by processing fatty acids. Fatty acid metabolism leads to ketone generation, which the body can then use directly as energy in the case of the brain and heart, or shuttle into adenosine-5-triphosphate production. The subsequent accumulation of ketones in the blood decreases plasma pH.[12]

Insulin deficiency creates a metabolic state that is interpreted as starvation by the body. In response to the decreased intracellular glucose concentrations, the body is forced to tap into energy stores by processing fatty acids.

Hyperglycemia further worsens the insulin-deficient state by promoting dehydration. The increased concentration of glucose increases the plasma osmolarity, in turn, having a diuretic effect. The polyuria caused by this osmotic diuresis prevents bicarbonate from being reabsorbed by the

kidney tubules, further concentrating the ketones and glucose circulating throughout the body. The combination of this acidotic state and severe dehydration in the context of insulin deficiency is termed *diabetic ketoacidosis* (DKA).[12]

Overall, DKA is less common than hypoglycemic episodes during pregnancy, yet it poses an increased risk to the fetus.[3] DKA currently affects 1% to 3% of pregnancies with pregestational diabetes.[13] Due to decreased insulin sensitivity and overall catabolic state seen in pregnancy, DKA may develop faster than in nonpregnant states. The decreased levels of plasma bicarbonate present in pregnancy as a physiologic response to increased minute ventilation further decrease the body's buffering capacity. Infections, such as upper respiratory and urinary tract infections, along with defective insulin pumps, antenatal corticosteroids, and β-mimetic tocolytics, can precipitate episodes of DKA. Although maternal death due to DKA is rare, fetal demise has been reported in up to 35% of cases.[13] In general, correction of the maternal metabolic derangement will result in correction of fetal acidosis and may allow for continuation of gestation, or, if at term, deliver under more optimal conditions than if immediate delivery in the midst of maternal DKA were undertaken.

Although maternal death due to DKA is rare, fetal demise has been reported in up to 35% of cases.

Treating DKA in Pregnancy

- Obtain arterial blood gas, blood glucose, electrolytes, and ketones every hour
- IV insulin: 0.2-0.4 U/kg loading dose, then 2-10 U/h
- Fluid replacement: Goal 4-6 L over 24 h; replace 1 L in first hour, then 250 mL/h of NS
- Start 5% dextrose/NS when blood glucose falls below 250 mg/dL
- Potassium replacement: If reduced or normal at presentation, replace at 15-20 mEq/h
- If pH $<$ 7.10, administer 1 ampule bicarbonate in 1 L of ½NS, normal saline.

Retinopathy

Diabetic retinopathy is the number one cause of new-onset blindness among Americans between the ages of 20 and 74 years. Although only 60% of patients with type 2 diabetes develop retinopathy, nearly all T1DM patients of disease duration greater than 20 years will have some retinal damage. The chronic hyperglycemic state observed in these insulin-deficient patients increases the amount of glucose that permeates into sensitive endothelial cells that line capillaries and blood vessels. In the retina, cells that support the vascular supply, termed *pericytes*, are particularly susceptible to chronic hyperglycemia. Continuous damage to endothelial tissue leads to vascular sclerosis and edema, and ultimately vascular compromise. In response to damage, ischemic retinal tissue secretes proangiogenic growth factors, such as vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) in an attempt to restore blood flow. It is this neovascularization in response to ischemia that leads to proliferative diabetic retinopathy. The combination of neovascularization around structures such as the fovea and ischemia throughout the retina leads to blindness, retinal detachment, and intraocular hemorrhages.[14]

Long-standing concern regarding the increased rate of progression of diabetic retinopathy during early pregnancy, especially when establishing rapid glycemic control with insulin, has been of recent debate. A study published by the National Eye Institute[15] concluded that the increased risk of progression cannot be explained solely by rapid normalization of glucose. The authors argued that the poor glycemic control, requiring rapid normalization, predisposes patients to the retinal changes.[15] Even with the initial progression of disease that is observed with normalization, tight control of plasma glucose levels lowers the overall long-term progression when compared with more liberal management.[13] The implications of new insulin analogs and their effects on progression of retinopathy are of further concern due to their increased insulin growth factor (IGF) activity. Initial studies on insulin lispro have shown no increase in the progression of retinopathy compared with patients receiving regular insulin.[16] Laser therapy during pregnancy for treatment of proliferative retinopathy is an appropriate option for management. There is a debate over whether to allow a vaginal delivery in cases of suboptimally treated proliferative retinopathy. There are insufficient data on this topic; therefore, it is advisable to treat patients in an individualized manner in collaboration with input from endocrinology and ophthalmology.

Nephropathy

Diabetic nephropathy can be described as a combination of structural changes in the interstitial and glomerular compartments of the kidney, which can ultimately lead to end-stage renal disease. These changes can occur in parallel or individually, and progress in varying rates. Thickening of the glomerular and tubular basement membranes and hyalinization of the arteriolar supply have all been shown to occur in diabetic patients and hinder renal function. Expansion of the mesangium due to accumulation of extracellular matrix (ECM) components decreases the surface area available for filtration in the glomerular compartment. It is the accumulation of ECM components like collagen, laminin, and fibronectin that can be ultimately held responsible for the development of clinical diabetic nephropathy.[17]

The increase in renal load inherent to pregnancy, combined with heightened risk of preeclampsia in diabetic pregnancies, further increases the propensity for renal damage. The American Congress of Obstetricians and Gynecologists (ACOG) Practice Bulletin cautions practitioners regarding progression of nephropathy to end-stage renal disease in patients with creatinine levels greater than 1.5 mg/dL or overt proteinuria (> 3 g protein/day). Renoprotective medications commonly used in diabetic patients are contraindicated in pregnancy due to their teratogenic nature. Alternative medications such as methyl-dopa are used for their antihypertensive and renoprotective properties. A recent study showed that early and aggressive antihypertensive therapy with methyl-dopa in patients with preexisting renal disease improved fetal outcome.[18]

Preeclampsia

Preeclampsia is characterized by gestational hypertension (blood pressure > 140/90 mm Hg) and proteinuria (urinary protein > 0.3 g/24 h) with onset after 20 weeks' gestation. Although the precise etiology of this disease is unknown, various theories including vascular damage, immunologic phenomena, and dietary deficiencies are among the leading suspects.[6]

Pregestational diabetes mellitus, as seen with T1DM patients, is a well-known risk factor for preeclampsia.[19] The risk of developing preeclampsia in gravid T1DM patients is between 12% to 15%, compared with 5% to 7% in the general population.[3,19] In patients with preexisting nephropathy the risk rises to as much as 50%.[13]

Preterm Labor

T1DM patients have an increased risk of preterm delivery. A recent cohort study[20] demonstrated that preterm delivery rates were as high as 24% in T1DM patients. This value agrees with those previously reported, which ranged between 26.2% and 31.1%.[19,21] The indicated preterm delivery rate in the cohort study was 15%, compared with values of 16.5% and 21.9% in the 2 older studies. Spontaneous preterm deliveries were also elevated at 9%.[20]

Previous studies have been limited due to the lack of controlled variables such as diabetes complications, preconception glycemic control, glycemic control throughout the pregnancy, and new fetal-monitoring modalities. By following these parameters, the physicians behind the recently published cohort study were able to conclude that HbA_1C at delivery was significantly associated with spontaneous preterm delivery. The progression of nephropathy and development of preeclampsia, alongside HbA_1C levels, were all significantly associated with preterm delivery. Interestingly, these authors did not note macrosomia and polyhydramnios to be significantly correlated with spontaneous preterm delivery.[20]

Blood Glucose and HbA_1C

%	mg/dL
6.0	126
6.5	140
7.0	154
7.5	169
8.0	183
8.5	197
9.0	212
10.0	240

HbA_1C, glycosylated hemoglobin levels

Fetal Outcome

The rate of fetal malformations (7.7% vs 7.3%) and spontaneous abortions (4.3% vs 2.2%) approaches that of the general population with good glycemic control.[22] In a study by Hanson and colleagues,[22] a direct relationship between HbA_1C and the rate of fetal malformation was noted. Patients who maintained HbA_1C levels between 5% and 6% had a normal pregnancy, whereas those with levels > 10.1% showed an incidence of neonatal malformation between 20% and 25%.[22] The prevalence of macrosomia in infants of diabetic mothers has remained constant throughout the years, even with tighter glucose control and advances in insulin therapy.[13] The risk of shoulder dystocia during vaginal delivery doubles when fetal weight is > 4000 g.[23]

Management

Preconception

Successful management of pregnancy in a T1DM patient begins before conception. Research indicates that the implementation of preconception counseling, emphasizing strict glycemic control before and throughout pregnancy, reduces the rate of perinatal mortality and malformations.[24] The 2008 bulletin from the National

Institute for Health and Clinical Excellence recommends that preconception counseling be offered to all patients with diabetes. Physicians are advised to guide patients on achieving personalized glycemic control goals, increasing the frequency of glucose monitoring, reducing their HbA_1C levels, and recommend avoiding pregnancy if said level is $>$ 10%.[25] Other sources suggest deferring pregnancy until HbA_1C levels are $<$ 8%, as this margin is associated with better outcomes.[22] The latest ACOG Practice Bulletin also suggests a thorough evaluation aimed at uncovering any underlying vascular damage. This includes retinal examination by an ophthalmologist, 24-hour urine protein and creatinine clearance, and electrocardiography.[23]

Dietary Guidelines

Dietary recommendations by ACOG emphasize the need for carbohydrate counting and bedtime snacks to prevent nocturnal hypoglycemia. These guidelines allow for only a 300 kcal/day increase from basal calorie consumption, with a target of 30 to 35 kcal/kg/day in females with normal body weight. In patients weighing $>$ 120% of their ideal body weight, the caloric requirements should be restricted to 24 kcal/kg/day. The majority of the diet should be composed of complex, high-fiber foods.[23] Patients should aim to achieve pre-meal plasma glucose levels of $<$ 100 mg/dL, followed by 1-hour postprandial levels $\leq$140 mg/dL, and 2-hour levels $<$ 120 mg/dL. HbA_1C levels should remain below 6% and overnight values should be controlled following the same guidelines, with values no lower than 60 mg/dL.[3,23] HbA_1C values can be obtained every month, in contrast to the standard 3-month period, due to increased red blood cell production and turnover during pregnancy.[26]

Glycemic Control

Insulin management is usually tailored to the individual patient. Most advocate the use of a regular or quick-acting insulin regimen to cover mealtime glucose changes, and an intermediate or long-acting insulin bolus twice a day.[8,26,27] A randomized, controlled trial published in the *British Medical Journal* demonstrated that the 4-times daily regimen improved maternal glycemic control and reduced neonatal complications, compared with the twice-daily regimen. In addition, the rates of maternal complications during the pregnancy were the same between both dosing regimens.[28] The twice-daily regimen allows for increased frequency of hyperglycemia and nocturnal hypoglycemic events. Continuous infusion methods using insulin pumps do not significantly improve outcome, and are suggested only for pregnancies complicated with difficult glycemic control and high White classification.[29]

Insulin management is usually tailored to the individual patient. Most advocate the use of a regular or quick-acting insulin regimen to cover mealtime glucose changes, and an intermediate or long-acting insulin bolus twice a day.

Recent developments in alternative insulin formulations have increased the options patients and physicians have at their disposal. Although regular human insulin still serves as the benchmark for mealtime boluses, the rapid-onset insulin analogs lispro and aspart have become drugs of choice. Most clinical retrospective trials show no difference in the perinatal outcomes between regimens using human insulin or insulin lispro. Instead these studies showed that better postprandial glucose control was achieved using the rapid-onset formulation.[30] Insulin aspart showed similar results in a recent study when used in combination with isophane insulin (NPH) as the intermediate-acting insulin. This study demonstrated a tendency toward better postprandial glycemic control and a similar maternal profile when compared with human insulin.[31]

Long-acting insulin formulations have also been developed in recent years. Insulin glargine and insulin detemir have come onto the market as long-acting, peakless formulations. Initial studies comparing once-daily glargine against a twice-daily NPH demonstrated no difference in glycemic control and no changes in maternal/fetal outcome.[32-34] A recent prospective study consisting of 56 pregestational diabetes patients showed improved maternal and perinatal outcomes when compared with patients receiving NPH.[35] In this study, all patients received insulin lispro as their prandial bolus insulin.

There have been recent concerns over the safety of insulin glargine during pregnancy due to possible mitogenic properties in the unborn fetus. Insulin glargine has been shown to have between 6- and 18-fold greater IGF-receptor binding affinity in osteosarcoma cell lines.[36] Interestingly, a recent retrospective study involving 102 pregnancies of T1DM mothers, all of whom used insulin glargine throughout their pregnancy, showed no increase in congenital malformations or perinatal complications.[37] Transplacental perfusion studies have shown that, if administered at therapeutic levels, insulin glargine does not cross the placenta.[38]

Preconception	• Initiate intensive glucose management with a goal of $A_1C < 6.1\%$. Dietary and diabetic counseling should be offered. Patients with $A_1C > 10\%$ should be counseled against pregnancy. • Comprehensive ophthalmologic examination should be performed. • Baseline serum creatinine and urine albumin/creatinine ratio should be obtained. Counsel patient regarding risk of ESRD if serum creatinine >1.5 mg/dL. Refer to nephrologist if adequate. • Thyroid function tests should also be performed. • Suggest daily multivitamin with at least 400 μg of folic acid.
Gestation	• Adequate glycemic control should be maintained. Diabetic counseling should be readily available to help manage rapidly changing insulin requirements. Consider insulin pump if proper glucose management is not attainable. • Repeat ophthalmologic assessment at 16-18 weeks if baseline retinal examination was abnormal. If normal at baseline, repeat at 28 weeks. • Fetal anatomy scan with 4-chamber cardiac imaging should be performed at 18-20 weeks. • Fetal ultrasound to assess growth and amniotic fluid levels should be performed every 4 weeks after 28 of weeks gestation. • Biweekly fetal monitoring (NST) can be started at 32 weeks of gestation, or earlier if warranted. • Daily fetal movement counts should be encouraged starting at 28 weeks.
Labor and Delivery	• Cesarean delivery should be suggested if fetal size is estimated to be > 4500 g. • Fetal lung maturity should be assessed via L/S ratio and phosphatydilglycerol if delivery is planned before 39 weeks. • Fetal and maternal well-being should be considered when deciding timing and method of delivery. • During labor intravenous access should be established and maintained with normal saline. • Blood glucose should be titrated to a level of approximately 100 mg/dL with 5% IV dextrose and/or IV regular insulin. • Bedside blood glucose should be checked every hour.
Postpartum	• Insulin may be reduced to 50% of predelivery requirements after adequate oral intake. • Insulin replacement should be tailored to achieve proper glycemic control and reduce hypoglycemic events. • Breastfeeding is encouraged, but patient should be counseled about increased risk of hypoglycemia with breastfeeding.

ESRD, end-stage renal disease; IV, intravenous; L/S, lecithin/sphingomyelin; NST, non-stress test.

Insulin detemir, although also a long-acting, peakless formulation, requires twice-daily dosing due to a decreased duration of action.[30] Studies to determine the efficacy of insulin detemir compared with NPH are ongoing. Even with data supporting their safety and efficacy, neither insulin glargine nor insulin detemir is currently indicated for use during pregnancy.[30]

Titration of plasma glucose levels during labor can be achieved using intravenous (IV) infusions of regular insulin and 5% dextrose. If labor is planned, ACOG guidelines indicate that the morning dose of insulin should be withheld, and IV dosing should not be initiated until blood glucose reaches 110 mg/mL. At that point, regular insulin should be administered at a 1.25 U/hour rate to keep plasma glucose levels below 110 mg/dL. If levels fall to 70 mg/dL or below, a 5% dextrose solution should be started at a rate of 100-150 mL/hour. Blood glucose levels should be measured at bedside every hour.[23,27]

After delivery, insulin sensitivity increases greatly due to the rapid decline of hormonal influences.[27] Patients quickly return to their pregravid insulin requirements, and insulin replacement may be restarted at 50% of the gravid dosage as soon as oral nutrient intake resumes (Table 3).[23,25,27]

Table 3
Insulin Replacement

Mealtime Bolus				
Insulin	**Source**	**Onset**	**Duration (h)**	**Peak (h)**
Novolin/Humulin R	Human	30 min	5-8	2-5
Lispro	Synthetic	15 min	4-5	0.5-1.5
Aspart	Synthetic	15 min	3-5	1-3
Intermediate/Long-Acting:				
NPH	Human	1-2 h	18-24	6-12
Glargine	Synthetic	1 h	24	None
Detemir	Synthetic	1-2 h	24 (12)	None

NPH, isophane insulin.
Data from Gabbe SG et al[6] and Torlone E et al.[30]

Conclusions

T1DM affects a small percentage of pregnancies each year, but poses great risk to the pregnant mother and developing fetus. Intensive counseling before conception and throughout pregnancy seems to decrease the probability of complications and fetal malformations. Individualized approaches to glycemic control and frequent follow-up visits increase the complexity of management, particularly in the noncompliant patient.

Recent advances in the management of T1DM have started to cross into the field of obstetrics. Although some novel insulin formulations lack US Food and Drug Administration approval for use in pregnancy, their use is widely accepted. Further research is needed to address the safety and efficacy of new insulin, as their ease-of-use should increase compliance and ultimately improve glycemic control. ■

References

1. Centers for Disease Control. *National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007*. Atlanta, GA: Centers for Disease Control and Prevention, Department of Health and Human Services; 2008.
2. Gibbs RS, Danforth DN. *Danforth's Obstetrics and Gynecology*. 10th ed. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; 2008.
3. Garner P. Type I diabetes mellitus and pregnancy. *Lancet*. 1995;346:157-161.
4. White P. Pregnancy complicating diabetes. *Am J Med*. 1949;7:609-616.
5. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet*. 2001;358:221-229.
6. Gabbe SG, Niebyl JR, Simpson JL. *Obstetrics: Normal and Problem Pregnancies*. 5th ed. Philadelphia, PA: Churchill Livingstone/Elsevier; 2007.
7. Kirwan JP, Hauguel-De Mouzon S, Lepercq J, et al. TNF-alpha is a predictor of insulin resistance in human pregnancy. *Diabetes*. 2002;51:2207-2213.
8. Weiss PA, Hofmann H. Intensified conventional insulin therapy for the pregnant diabetic patient. *Obstet Gynecol*. 1984;64:629-637.
9. García-Patterson A, Gich I, Amini SB, et al. Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. *Diabetologia*. 2010;53:446-451.
10. Nielsen LR, Rehfeld JF, Pedersen-Bjergaard U, et al. Pregnancy-induced rise in serum C-peptide concentrations in women with type 1 diabetes. *Diabetes Care*. 2009;32:1052-1057.

Main Points

- Before insulin therapy, infertility was the most common consequence of type 1 diabetes mellitus (T1DM) on reproductive-age women. When pregnancy did occur, fetal and neonatal mortality was as high as 60%. Aggressive maternal-fetal management, advances in insulin therapy, and improvements in neonatal intensive care units have decreased this figure to 2% to 5%.
- T1DM patients are at increased risk for complications such as hypoglycemia, diabetic ketoacidosis, retinopathy, nephropathy, preeclampsia, and preterm labor.
- Successful management of pregnancy in T1DM patients begins before conception with the implementation of preconception counseling that emphasizes the need for strict glycemic control before and throughout pregnancy. Physicians should guide patients on achieving personalized glycemic control goals, increasing the frequency of glucose monitoring, reducing their glycosylated hemoglobin levels levels, and recommend the avoidance of pregnancy if levels are $>$ 10%.
- Dietary recommendations from the American College of Obstetrics and Gynecology emphasize the need for carbohydrate counting and bedtime snacks to prevent nocturnal hypoglycemia. Guidelines allow for only a 300 kcal/day increase from basal calorie consumption, with a target of 30 to 35 kcal/kg/day in women with normal body weight and 24 kcal/kg/day for women weighing $>$ 120% of ideal body weight.
- Recent advances in the management of T1DM have begun to cross into the obstetrics domain. Although novel insulin formulations lack US Food and Drug Administration approval for use in pregnancy, their use is widely accepted. Additional research is needed to address the safety and efficacy of new insulin, as their ease-of-use should increase compliance and improve glycemic control.

11. Rosenn BM, Miodovnik M, Khoury JC, Siddiqi TA. Counterregulatory hormonal responses to hypoglycemia during pregnancy. *Obstet Gynecol*. 1996;87:568-574.
12. Cecil RL, Goldman L, Ausiello DA. *Cecil Medicine*. 23rd ed. Philadelphia: Saunders Elsevier; 2008.
13. Reece EA, Coustan DR, Gabbe SG. *Diabetes in Women: Adolescence, Pregnancy, and Menopause*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004.
14. Kronenberg H, Williams RH. *Williams Textbook of Endocrinology*. 11th ed. Philadelphia: Saunders/Elsevier; 2008.
15. Chew EY, Mills JL, Metzger BE, et al. Metabolic control and progression of retinopathy. The Diabetes in Early Pregnancy Study. National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. *Diabetes Care*. 1995;18:631-637.
16. Loukovaara S, Immonen I, Teramo KA, Kaaja R. Progression of retinopathy during pregnancy in type 1 diabetic women treated with insulin lispro. *Diabetes Care*. 2003;26:1193-1198.
17. Brenner BM, Rector FC. *Brenner & Rector's The Kidney*. 8th ed. Philadelphia: Saunders Elsevier; 2008.
18. Nielsen LR, Damm P, Mathiesen ER. Improved pregnancy outcome in type 1 diabetic women with microalbuminuria or diabetic nephropathy: effect of intensified antihypertensive therapy? *Diabetes Care*. 2009;32:38-44.
19. Sibai BM, Caritis SN, Hauth JC, et al. Preterm delivery in women with pregestational diabetes mellitus or chronic hypertension relative to women with uncomplicated pregnancies. The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol*. 2000;183:1520-1524.
20. Lepercq J, Coste J, Theau A, et al. Factors associated with preterm delivery in women with type 1 diabetes: a cohort study. *Diabetes Care*. 2004;27:2824-2828.
21. Greene MF, Hare JW, Krache M, et al. Prematurity among insulin-requiring diabetic gravid women. *Am J Obstet Gynecol*. 1989;161:106-111.
22. Hanson U, Persson B, Thunell S. Relationship between haemoglobin A1C in early type 1 (insulin-dependent) diabetic pregnancy and the occurrence of spontaneous abortion and fetal malformation in Sweden. *Diabetologia*. 1990;33:100-104.
23. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 60, March 2005. Pregestational diabetes mellitus. *Obstet Gynecol*. 2005;105:675-685.
24. McElvy SS, Miodovnik M, Rosenn B, et al. A focused preconceptional and early pregnancy program in women with type 1 diabetes reduces perinatal mortality and malformation rates to general population levels. *J Matern Fetal Med*. 2000;9:14-20.
25. Guideline Development Group. Management of diabetes from preconception to the postnatal period: summary of NICE guidance. *BMJ*. 2008;336:714-717.
26. Jovanovic L. Screening and diagnosis of gestational diabetes. In: *Up to Date*. Rose BD, ed. Waltham, MA: UpToDate; 2009.
27. Hare JW. Insulin management of type I and type II diabetes in pregnancy. *Clin Obstet Gynecol*. 1991;34:494-504.
28. Nachum Z, Ben-Shlomo I, Weiner E, Shalev E. Twice daily versus four times daily insulin dose regimens for diabetes in pregnancy: randomised controlled trial. *BMJ*. 1999;319:1223-1227.
29. Lapolla A, Dalfrà MG, Masin M, et al. Analysis of outcome of pregnancy in type 1 diabetics treated with insulin pump or conventional insulin therapy. *Acta Diabetol*. 2003;40:143-149.
30. Torlone E, Di Cianni G, Mannino D, Lapolla A. Insulin analogs and pregnancy: an update. *Acta Diabetol*. 2009;46:163-172.
31. Mathiesen ER, Kinsley B, Amiel SA, et al. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes Care*. 2007;30:771-776.
32. Di Cianni G, Torlone E, Lencioni C, et al. Perinatal outcomes associated with the use of glargine during pregnancy. *Diabet Med*. 2008;25:993-996.
33. Gallen IW, Jaap A, Roland JM, Chirayath HH. Survey of glargine use in 115 pregnant women with Type 1 diabetes. *Diabet Med*. 2008;25:165-169.
34. Imbergamo MP, Amato MC, Sciortino G, et al. Use of glargine in pregnant women with type 1 diabetes mellitus: a case-control study. *Clin Ther*. 2008;30:1476-1484.
35. Negrato CA, Rafacho A, Negrato G, et al. Glargine vs. NPH insulin therapy in pregnancies complicated by diabetes: an observational cohort study. *Diabetes Res Clin Pract*. 2010;89:46-51.
36. Kurtzhals P, Schäffer L, Sørensen A, et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes*. 2000;49:999-1005.
37. Lepercq J, Jacqueminet S, Hieronimus S, et al. Use of insulin glargine throughout pregnancy in 102 women with type 1 diabetes. *Diabetes Metab*. 2010;36:209-212.
38. Pollex EK, Feig DS, Lubetsky A, et al. Insulin glargine safety in pregnancy: a transplacental transfer study. *Diabetes Care*. 2010;33:29-33.